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October 26, 1999

Dockets Management Branch (HFA – 305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 99D-2635
Guidance for Industry
ANDAs : Blend Uniformity Analysis

Dear Sir:

This is in response to FDA's request for comments on the Draft Guidance entitled "Guidance for Industry, ANDAs: Blend Uniformity Analysis" which appeared in the Federal Register vol. 64, No. 166, p.46917. Please consider the following issues.

1. According to the Supplemenentary Information provided in the Federal Register "This draft guidance is intended to provide recommendations on when BUA (Blend Uniformity Analysis) should be performed. " However, the guidance is directed only to "original ANDA's and supplemental ANDA's for formulation and process changes". By the act of omission, the guidance does not apply to original NDA's and supplemental NDA's for formulation and process changes.

   In general, ANDAs, by definition, can only exist after the patents for NDAs have expired. If the Blend Uniformity Guidance is accepted as written, this would mean that the consumer would need to wait until the patents expire before the scientific and regulatory rational given for this Guidance would apply. In other words, during the NDA protection phase of a drug product (i.e. 5 – 12 years), the consumer would need to assume a safety risk regarding the consistency of a drug product since there would be no BUA requirement for NDA drug products. To restore the scientific creditability of FDA between the various divisions within CDER, FDA should withdraw this guidance as written or include NDA products in this guidance.

2. The guidance states "The recommended sample size of the blend material is no more than three times the weight of an individual dose. If the firm experiences problems in collecting small samples equivalent to 1 to 3 dosage units and demonstrates that small samples gives lower values for BUA due to sampling bias, lager samples (usually no more than 10 dosage units) can be collected." Unfortunately, samples size of 10 dosage units may reduce sampling bias but what would be the meaning of the results. A blend found to be uniform with a sample size of 10 units does not tell us much about its actual uniformity of one unit.

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We agree with FDA's acknowledgement of the existence of blend sampling bias. Some factors which may contribute to this bias are: the physical characteristics of the blend itself, e.g. whether it is sticky, fluffy, or waxy; the electrostatic effect of the powder during blend sampling and handling may result in possible segregation of particles during filling of the thief chamber; the sample thief design and the sampling techniques may prevent collection of representative sample of the final dosage form; single unit dose sampling may be too small to handle; etc. Therefore, it is possible that the blend uniformity test data may not represent the true uniformity of the blend due to variation introduced during blend sampling and handling. We believe FDA's previous communication to PDA (PDA Journal of Pharmaceutical Science and Technology, vol. 51, No. 3 p. S84-S87, 1997) allowing extensive tablet (or capsule) content uniformity testing is still a valid scientific approach when blend sampling bias is observed.

3. The draft Guidance does not define a mechanism for Industry to remove the requirement to perform BUA if data are obtained to demonstrate that this type of testing is not necessary. OGD initially had proposed that BUA could be deleted if approved by FDA. However, it has never been clear if this means by approval from the District Office or from the Washington D.C. office.

   During process validation procedures and initial commercial batch production, a company gains confidence that the manufacturing process is performing as anticipated and is under control. BUA document the consistency of a manufacturing process. Manufacturing consistency assures that the drug product which was found to be bioequivalent when the application was approved is identically to the bioequivalent product released today.

   Unless the manufacturing processes is significantly changed, i.e. the use of different manufacturing equipment, a change in vendor of drug substance, etc., at some point the executed batch record and corresponding finished product analysis should be able to document that the manufacturing procedure is consistently and correctly performed. At this point, a mechanism should be available to industry to substitute routine batch record documentation for BUA.

Thank you for the opportunity to comment on the proposed rule.

Sincerely,

Ernest Lengle, Ph.D.

Ernest Lengle, Ph.D.
Sr. Director
Regulatory Affairs

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